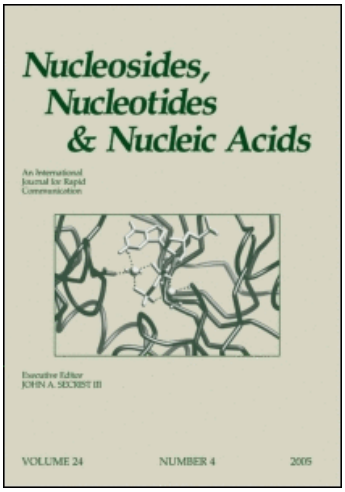

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First Synthesis of Double Headed 1,3,4-Oxadiazino[6,5-*b*]indole Acyclo *C*-Nucleosides

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ABSTRACT

Condensation of 1,3-dihydro-2,3-dioxo-2*H*-indoles **(1a–c)** with galactaric acid bis hydrazide **(2)** gave the corresponding galactaric acid bis[2-(1,2-dihydro-2-oxo-3*H*-indol-3-ylidene)hydrazides] **(3a–c)**. Acetylation of the latter compounds with acetic anhydride in the presence of pyridine at ambient temperature gave the 2,3,4,5-tetra-*O*-acetylgalactaric acid bis[2-(1,2-dihydro-2-oxo-1-substituted-3*H*-indol-3-ylidene)hydrazides] **(4b–d)**. Heterocyclization of the tetra-*O*-acetates **4b–d** by heating with thionyl chloride afforded the double headed acyclo *C*-nucleosides: 1,2,3,4-tetra-*O*-acetyl-1,4-bis{9-substituted-1,3,4-oxadiazino[6,5-*b*]indol-2-yl-1-ium}-*galacto*-tetritol dichlorides **(5b–d)**. Structures of the prepared compounds were elucidated from their spectral properties.

Key Words: Isatin; Galactaric acid bis hydrazide; Double headed acyclo *C*-nucleosides; 1,3,4,-oxadiazino [6,5-b]indoles.

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INTRODUCTION

Acyclo *C*-nucleosides represent an important class of compounds[1–7] characterized by an acyclic sugar moiety attached to heterocycle through a carbon-carbon bond. Many synthetic acyclo *C*-nucleosides have also been found to possess important biological activites including antivral,[8] antibacterial,[9] antifungal[10] and protein kinase inhibition activity.[11] Double headed acyclo *C*-nucleosides carrying imidazoline,[12] 1,2,4-triazole,[10,13] 1,3,4-oxadiazole,[14,15] 1,3,4-thiadiazole,[10] 1,2,4-triazolo[3, 4-*b*]-1,3,4-thiadiazole,[13,16] benzimidazole,[17] quinazoline[18] and 1,3-benzoxazine[18] rings were reported in the literature. 1,3,4-Oxadiazino[6,5-*b*]indoles are known to possess antifungal,[19,20] antibacterial,[20,21] antihistaminic[20] and antimuscarinic[20] activity. The incorporation of a tetritolyl moiety in the 1,3,4-oxadiazino[6,5-*b*]indole system has not been reported. Therefor, the present study targeted the synthesis of the novel title compounds as a part of a program addressed to prepare new acyclo *C*-nucleosides.[10,12,22–24] The prepared title acyclo *C*-nucleosides are expected to possess potential biological activites due to the resistance of the *C*-glycosidic moiety to hydrolytic or enzymatic cleavage[25] as well as their enhanced hydrophilicity which leads to increased transportation to biological systems.

RESULTS AND DISCUSSION

Condensation of two molar equivalents of 1,3-dihydro-2,3-dioxo-2*H*-indole **(1a)** or its 1-alkyl derivatives, namely: 1,3-dihydro-1-methyl-2,3-dioxo-2*H*-indole **(1b)**[26] and 1-ethyl-1,3-dihydro-2,3-dioxo-2*H*-indole **(1c)**[27] with one molar equivalent of galactaric acid bishydrazide **(2)**[28] gave the corresponding galactaric acid bis[2-(1,2-dihydro-2-oxo-3*H*-indol-3-ylidene)hydrazides] **(3a–c)**.

Treatment of compounds **3a–b** with acetic anhydride in the presence of pyridine at ambient temperature resulted in acetylation of the galactaroyl OH groups as well as the NH of the two indole rings in the case of compound **3a**. The spectral data are in agreement with the 2,3,4,5-tetra-*O*-acetylgalactaric acid bis[2-(1,2-dihydro-2-oxo-1-substituted-3*H*-indol-3-ylidene)hydrazide] structures **(4b–d)**.

Heterocyclization of the tetra-*O*-acetates **4b–d** by heating with thionyl chloride afforded crystalline products lacking the NH absorption in the IR region as well as two hydrazido proton signals characteristic of the parent compounds in the ^{1}H NMR spectral. These spectroscopic data together with the elemental analyses of the cyclization products are compatible with the double headed acyclo *C*-nucleoside structures: 1,2,3,4-tetra-*O*-acetyl-1,4-bis{9-substituted-1,3,4-oxadiazino[6,5-*b*]indol-2-yl-1-ium}-*galacto*-tetritol dichlorides **(5b–d)** rather than the hydrazidoyl structures **6b–d**. Had the hydrazidoyl chloride structure been correct, the IR spectra of compounds **6b** and **6c** would have revealed two carbonyl absorptions; one due to an amide group and the other due to the *O*-acetyl groups. The obtained IR spectra contained only one carbonyl absorption due to the *O*-acetyl groups which would reconcile with structures **5b** and **5c**. This result is in agreement with the work of Molina et al.[29] The mass spectrum of **5d** did not show its molecular ion peak, yet revealed a fragment at *m/z* 314 resulting from C1–C2 bond clevage of the sugar chain with loss of Cl^- and Ac^+ and another fragment at *m/z* 200 corresponding to the protonated formyl

heterocyclic moiety. The latter fragment is known to be diagnostic of *C*-nucleosides and acyclic *C*-nucleosides.[30]

EXPERIMENTAL

Melting points were determined on MEL-TEMP II melting point apparatus in open glass capillaries and are uncorrected. IR spectra were recorded as potassium bromide discs on a Pye-Unicam SP1025 spectrophotometer. Proton magnetic resonance (^{1}H NMR) spectra were carried out at ambient temperature (~25°C) with a Varian EM-390 or with a Brucker AC-250 spectrometer using tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were preformed on a Hewlett-Packard 5995 gas chromatography-mass spectrometer system. Homogeneity of the products and follow up of the reactions were checked by ascending thin-layer chromatography (TLC) on plates precoated with silica gel G (E. Merck; layer thickness 0.25 mm), used without pretreatment. All ratios of the solvent systems used were volume to volume (V/V); the solvent systems used were: 1) $CHCl_3$/MeOH (1:4) and 2) $CHCl_3$/MeOH (9:1); the distance of the solvent travel was 5 cm and the spots were visualized by exposure to iodine vapour for a few minutes. Elemental microanalyses were performed at the Microanalytical Unit, Cairo University, Cairo, Egypt (Scheme 1).

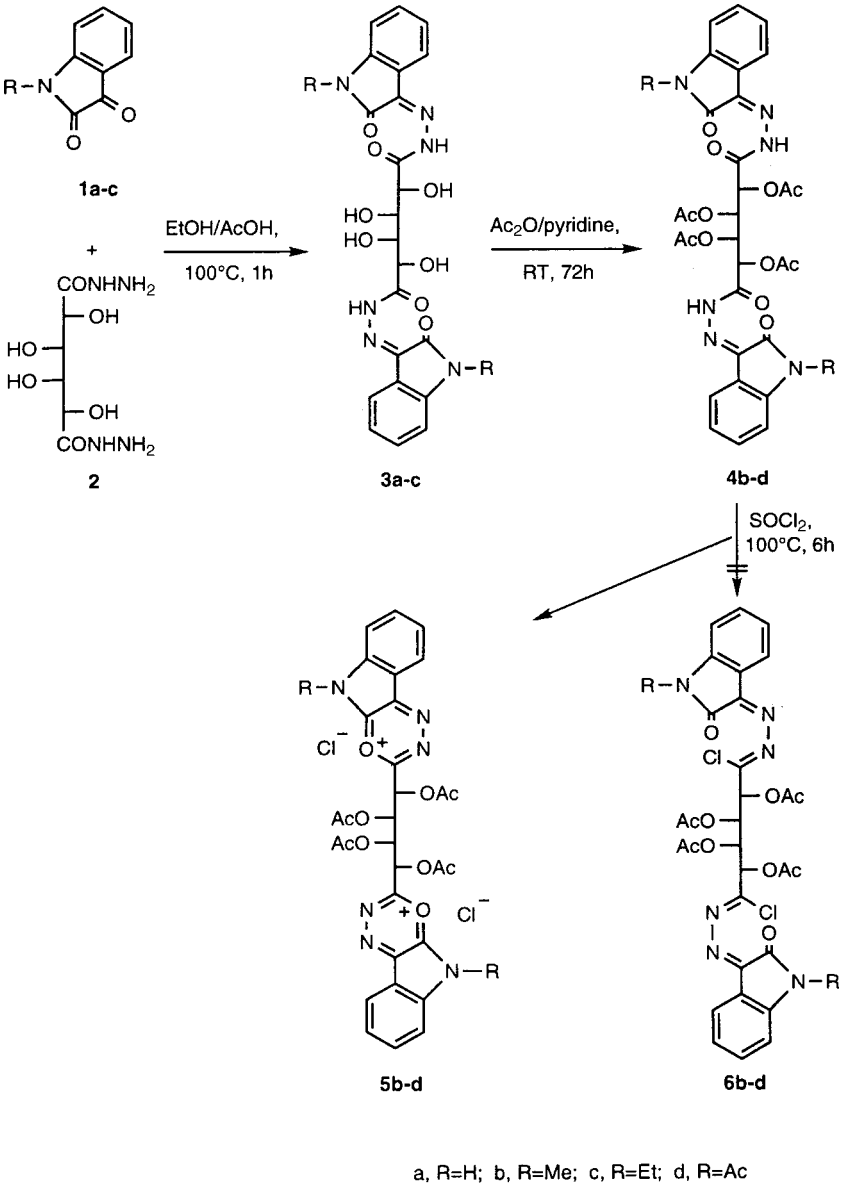
General procedure for the preparation of galactaric acid bis[2-(1,2-dihydro-2-oxo-3*H*-indol-3-ylidene)hydrazides] (3a–c). A solution of the appropriate 1,3-dihydro-2,3-dioxo-2*H*-indole (**1a–c**, 0.0084 mol) in ethanol (40 mL) containing 2 drops of acetic acid was added to a suspension of **2** (0.0042 mol) in ethanol (20 mL) and the reaction mixture was heated at reflux for 1 h with occasional stirring. After attaining room temperature, the product was filtered off and crystallized from water/ethanol-mixture. The following compounds were prepared:

Galactaric acid bis[2-(1,2-dihydro-2-oxo-3*H*-indol-3-ylidene)-hydrazide] (3a). Yield: 1.8 g (87%); orange crystals; m.p.: 255–257°C/dec; TLC: (A), R_F: 0.56; IR: 3262 (OH + NH), 1728, 1693 (CON), 1610 cm^{-1} (C = N); ^{1}H NMR (DMSO-d_6): δ 12.21, 11.92 (2 s, exchangeable, 2 NH each), 8.01, 7.62 (2 d, 2 H each, arom-H), 7.30–7.24 (m, 4 H, arom-H), 5.58, 5.08 (2 d, exchangeable, 2 OH each), 4.68, 3.93 (2 d, 2 H each, tetritoldi-1,4-yl).

Anal. Calcd. for $C_{22}H_{20}N_6O_8$: C, 53.23; H, 4.03; N, 16.94. Found: C, 53.33; H, 4.11; N, 17.08.

Galactaric acid bis[2-(1,2-dihydro-1-methyl-2-oxo-3*H*-indol-3-ylidene)hydrazide] (3b). Yield: 1.8 g (82%), orange yellow crystals; m.p.: 200–202°C/dec; TLC: (A), R_F: 0.61; IR: 3332 (OH + NH), 1725, 1703 (CON), 1607 cm^{-1} (C = N); ^{1}H NMR (DMSO-d_6): δ 12.21 (br s, exchangeable, 2 NH), 7.52–7.48, 7.18–7.14 (2 m, 4 H each, arom-H), 5.68, 5.08 (2 d, exchangeable, 2 OH each), 4.53, 3.85 (2 d, 2 H each, tetritoldi-1,4-yl), 3.73 (s, 6 H, $2CH_3$).

Anal. Calcd. for $C_{24}H_{24}N_6O_8$: C, 54.96; H, 4.58; N, 16.03. Found: C, 55.07; H, 4.61; N, 16.16.



Scheme 1. Steps of formation of double headed 1,3,4-oxadiazino [6,5-b]indole acyclo *C*-nucleosides.

Galactaric acid bis[2-(1-ethyl-1,2-dihydro-2-oxo-3*H*-indol-3-ylidene)hydrazide] (3c). Yield: 1.83 g (79%), orange yellow crystals; m.p.: 233–235°C/dec; TLC: (A), R_F: 0.62; IR: 3326 (OH + NH), 1727, 1694 (CON), 1611 cm^{-1} (C = N); ^1H NMR (DMSO-d_6): δ 11.86 (br s, exchangeable, 2 NH), 7.94, 7.69 (2 d, 2 H each, arom-H), 7.39–7.34 (m, 4 H, arom-H), 5.47, 4.68 (2 d, exchangeable, 2 OH each), 4.52 (q, 4 H, 2 CH_2CH_3), 4.40, 3.68 (2 d, 2 H each, tetritoldi-1,4-yl), 1.44 (t, 6H, 2 CH_2CH_3).

Anal. Calcd. for $C_{26}H_{28}N_6O_8$: C, 56.52; H, 5.07; N, 15.22. Found: C, 56.70; H, 5.11; N, 15.40.

General procedure for the preparation of 2,3,4,5-Tetra-*O*-acetyl-galactaric acid bis[2-(1,2-dihydro-2-oxo-1-substituted-3*H*-indol-3-ylidene)hydrazides] (4b–d). A mixture of the respective indolylidene galactaric acid hydrazide (**3a–c**, 0.002 mol). pyridine (5 mL) and acetic anhydride (15 mL) was stirred at room temperature for 72 h. The mixture was poured onto crushed ice and the product was filtered off, washed with water, dried and crystallized from a chloroform/ethanol-mixture. The following compounds were prepared:

2,3,4,5-Tetra-*O*-acetylgalactaric acid bis[2-(1,2-dihydro-1-methyl-2-oxo-3*H*-indol-3-ylidene)hydrazide] (4b). Yield: 1.0 g (76%); yellow crystals; m.p.: 348–350°C/dec; TLC (B), R_F: 0.64; IR: 3202 (NH), 1753 (OAc), 1730, 1692 (CON), 1616 cm^{-1} (C = N); ^{1}H NMR (DMSO-d_6): δ 12.26 (s, exchangeable, 2 NH), 8.26, 7.68 (2 d, 2 H each, arom-H), 7.44, 7.28 (2 t, 2 H each, arom-H), 6.16, 5.50 (2 s, 2 H each, tetritoldi-1,4-yl H), 3.75 (s, 6 H, 2 CH_3), 2.16, 2.10 (2 s, 6 H each, 4 OAc).

Anal. Calcd. for $C_{32}H_{32}N_6O_{12}$: C, 55.49; H, 4.62; N, 12.14. Found: C, 55.33; H, 4.75; N, 12.30.

2,3,4,5-Tetra-*O*-acetylgalactaric acid bis[2-(1-ethyl-1,2-dihydro-2-oxo-3*H*-indol-3-ylidene)hydrazide] (4c). Yield: 0.72 g (69%); yellow crystals; m.p.: 315–317°C/dec; TLC: (B), R_F: 0.63; IR: 3264 (NH), 1762 (OAc), 1736 (CON), 1607 cm^{-1} (C = N); ^{1}H NMR (DMSO-d_6): δ 12.93 (s, exchangeable, 2 NH), 7.68, 7.49 (2 d, 2 H each arom-H), 7.15–7.11 (m, 4 H, arom-H), 5.95, 5.31 (2 s, 2 H ech, tetritoldi-1,4-yl H), 4.04 (q, 4 H, 2 CH_2CH_3) 2.20, 1.91 (2s, 6 H each, 4 OAc), 1.29 (t, 6 H, 2 CH_2CH_3).

Anal. Calcd. for $C_{34}H_{36}N_6O_{12}$: C, 56.67; H, 5.00; N, 11.67. Found: C, 56.83; H, 4.88; N, 11.85.

2,3,4,5-Tetra-*O*-acetylgalactaric acid bis[2-(1-acetyl-1,2-dihydro-2-oxo-3*H*-indol-3-ylidene)hydrazide] (4d). Yield: 1.25 g (83%); yellow crystals; m.p.: 278–280°C/dec; TLC: (B), R_F: 0.62; IR: 3248 (NH), 1764 (OAc), 1717 (NAc), 1601 cm^{-1} (C = N); ^{1}H NMR (DMSO-d_6): δ 12.12 (br s, exchangeable, 2 NH), 7.51–7.48, 7.15–7.11 (2 m, 4 H each, arom-H), 6.17, 5.51 (2 s, 2 H each, tetritoldi-1,4-yl H), 3.25 (s, 6 H, 2 NAc), 2.26, 1.92 (2 s, 6 H each, 4 OAc).

Anal. Calcd. for $C_{34}H_{32}N_6O_{14}$: C, 54.55; H, 4.28; N, 11.23. Found: C, 54.67; H, 4.21; N, 11.40.

General procedure for the preparation of 1,2,3,4-Tetra-*O*-acetyl-1,4-bis{9-substituted-1,3,4-oxadiazino[6,5-*b*]indol-2-yl-1-ium}-*galacto*-tetritol dichlorides (5b–d). A mixture of the appropriate tetra-*O*-acetates **4b–d** (0.0014 mol) and thionyl chloride (30 mL) was heated under reflux for 6 h. Evaporation of the resulting solution under reduced pressure gave a residue which crystallized from a chloroform/ethanol-mixture. The following compounds were prepared:

1,2,3,4-Tetra-*O*-acetyl-1,4-bis{9-methyl-1,3,4-oxadiazino[6,5-*b*]-indol-2-yl-1-ium}-*galacto*-tetritol dichloride (5b). Yield: 0.75 g (71%), yellow crystals; m.p.: 256°C; TLC: (B), R_F: 0.53; IR: 1746 (OAc), 1615 cm^{-1} (C = N); ^{1}H NMR (DMSO-d_6): δ

7.51–7.48, 7.17–7.13 (2 m, 4 H each, arom-H), 5.85, 4.93 (2 s, 2 H each, tetritoldi-1,4-yl H), 2.83 (s, 6 H, 2 NCH_3), 2.49, 1.91 (2 s, 6 H each, 4 OAc).

Anal. Calcd. for $C_{32}H_{30}Cl_2N_6O_{10}$: C, 52.68; H, 4.12; N, 11.52. Found: C, 52.83; H, 3.99; N, 11.64.

1,2,3,4-Tetra-*O*-acetyl-1,4-bis{9-ethyl-1,3,4-oxadiazino[6,5-*b*]-indol-2-yl-1-ium}-*galacto*-tetritol dichloride (5c). Yield: 0.72 g (69%), yellow crystals; m.p.: 242°C; TLC: (B), R_F: 0.54; IR: 1742 (OAc), 1601 cm^{-1} (C = N); ^1H NMR (DMSO-d_6): δ 8.17, 7.54 (2 d, 2 H each, arom-H), 7.44, 7.33 (2 t, 2 H each, arom-H), 5.97, 4.88 (2 s, 2 H each, tetritoldi-1,4-yl H), 4.07 (q, 4 H, 2 CH_2CH_3), 2.49, 1.89 (2 s, 6 H each, 4 OAc), 1.24 (t, 6H, 2 CH_2CH_3).

Anal. Calcd. for $C_{34}H_{34}Cl_2N_6O_{10}$: C, 53.90; H, 4.49; N, 11.10. Found: C, 54.03; H, 4.60; N, 10.98.

1,2,3,4-Tetra-*O*-acetyl-1,4-bis{9-acetyl-1,3,4-oxadiazino[6,5-*b*]indol-2-yl-1-ium}-*galacto*-tetritol dichloride (5d). Yield: 0.8 g (76%); pale yellow crystals, m.p.: 252°C; TLC: (B), R_F: 0.49; IR: 1762 (OAc), 1739 (NAc), 1600 cm^{-1} (C = N); ^1H NMR (DMSO-d_6): δ 7.95 (d, 2 H, arom-H), 7.58–7.49 (m, 4 H, arm-H), 7.14 (t, 2 H, arom-H), 6.46, 5.58 (2 s, 2 H each, tetritoldi-1,4-yl H), 3.63 (s, 6 H, 2 NAc), 2.01, 1.97 (2 s, 6 H each, 4 OAc); MS: *m/z* (%) 314 (11.8), 242 (2.5), 200 (100), 170 (7.5).

Anal. Calcd. for $C_{34}H_{30}Cl_2N_6O_{12}$: C, 51.98; H, 30.82; N, 10.70. Found: C, 52.03; H, 3.91; N, 10.85.

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